



AB062. 234. Activation of an orphan nuclear receptor type 4A1 (NR4A1) represses pro-tumourogenic mediators in colorectal cancer

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Background: Inflammatory processes are pivotal pathogenic factors in colorectal cancer. NR4A1 receptors are emerging as regulators, concurrently repressing pro-inflammatory processes while activating resolution pathways. Whether this could improve cancer-related immune dysregulation is unknown.

Methods: Tumour and normal control tissue (n=20) obtained from patients undergoing colorectal resection were exposed to a NR4A1 agonist [cytosporone B (CsnB) 4–100 μ M] *ex vivo*. The supernatant was collected and RNA was extracted from tissues at 8 hours. A cytokine/chemokine array was used to examine 104 secreted proteins associated

with tumour inflammation, angiogenesis, fibrosis and growth factors. Quantitative enzyme-linked immunosorbent assay (ELISA) and qRT-PCR were used. Viability studies were performed on colorectal cancer cell lines for toxicity experiments.

Results: Cytokine/chemokine array analysis revealed 50/104 were increased in tumours including inflammatory (IL-8, TNF- α), angiogenic factors (angiopoietin 1, vascular endothelial growth factor), and growth factors (fibroblast growth factor 7, leukemia inhibitory factor). Of those, 30/50 were repressed by \geq 50% by the NR4A1 agonist. Multiple targets identified from the array were confirmed using quantitative ELISA and/or qRT-PCR including cytokines (e.g., IL-8, TNF- α , IL-23, IL-6), and chemokines (e.g., CCL3, CCL4, CCL20). Viability studies confirmed that CsnB is non-toxic.

Conclusions: Activation of an orphan nuclear receptor (NR4A1) represses pro-tumourogenic mediators such as cytokines, chemokines, growth factors, and angiogenic factors.

Keywords: Colorectal cancer; cytosporone B (CsnB); inflammation; NR4A1; orphan nuclear receptors

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